Annals of Clinical and Analytical Medicine
Original Research

Retrospective evaluation of patients with intracranial bleeding due to late vitamin K deficiency

Intracranial bleeding in Vitamin K deficiency

Barış Erdoğan[1], Duygu Ceman[2]
[1] Department of Neurosurgery, Şanlıurfa Train and Research Hospital, Şanlıurfa
[2] Department of Neurosurgery, Sancaktepe Şehit Prof.Dr.İlhan Varank Train and Research Hospital, Istanbul, Turkey

Abstract
Aim: In this study, we share our clinical experience and raise awareness about the importance of vitamin K prophylaxis. We evaluated
Material and Methods: We retrospectively evaluated the demographic characteristics, clinical and radiological findings of 9 patients with late vitamin K deficiency bleeding (VKDH) who were we followed in our clinic in 2020.
Results: It was determined that none of the 9 patients received postpartum vitamin K prophylaxis. The mean admission international normalized ratio (INR) of the patients was 4.2+1.1. Vitamin K was administered to all patients, and the mean of INR values decreased to 1.1+0.1. The most common complaint of the patients was convulsion (77.8%). Subarachnoid hemorrhage (SAH) + subdural hemorrhage (SDH) were detected in 4 patients, SAH+SDH+intraparenchymal hemorrhage (IPH) in 3 patients, SAH+IPH in 1 patient, and SAH in 1 patient. Surgery was performed on 3 patients. Two patients who were not operated died during their intensive care follow-up. Seven patients were discharged. Hemiplegia developed in 2 patients, and these patients were included in the physical therapy program.
Discussion: Late VKDB is most commonly seen between 2-12 weeks after birth. It causes serious morbidity and mortality. It is difficult to treat, time consuming and costly. It is possible to prevent late VKDB with intramuscular vitamin K prophylaxis after delivery.

Keywords
Hemorrhage, Prophylaxis Vitamin K

DOI: 10.4328/ACAM.21582 Received: 2023-01-10 Accepted: 2023-02-11 Published Online: 2023-02-22 Printed: 2023-03-25 Ann Clin Anal Med 2023;14(Suppl 1):S22-25
Corresponding Author: Barış Erdoğan, Department of Neurosurgery, Şanlıurfa Train and Research Hospital, Eyyubiye, Şanlıurfa, Turkey.
E-mail: dr.baris.erdogan@gmail.com P: +90 5462927177
Corresponding Author ORCID ID: https://orcid.org/0000-0003-4946-0748
This study was approved by the Ethics Committee of Harran University (Date: 2021-12-27, No: HRU/21.23.01).

Introduction

Vitamin K is a fat-soluble vitamin required for the synthesis of functional molecules of Factor II, Factor VII, Factor IX and Factor X produced by the liver. In the newborn period, enough vitamin K cannot be produced and stored. Among the reasons for this are low level of transfer of vitamin K through the placenta, low bioavailability due to the short half-life of liver stores, low level of vitamin K in breast milk compared to other milks, and insufficient production of intestinal flora due to immaturity. Bleeding due to coagulation disorder secondary to vitamin K deficiency is divided into two according to the time of occurrence. Bleeding between 24 hours and 14 days after birth (days 2-14) is called early vitamin K deficiency bleeding (VKDB) and bleeding between weeks 2-12 is called late VKDB [1-4].

VKDB can lead to a wide range of clinical presentations from mild nose bleeding, bleeding from the umbilical cord, gastrointestinal system bleeding to severe brain hemorrhages. An important feature of late VKDB is that intracranial hemorrhages are seen as the first sign of presentation. According to the study by Klironomy, et al., the incidence in those who did not receive prophylaxis was 4.4-7.2/100.000 [2, 5].

Late type VKDB can cause 30% to 60% of intracerebral hemorrhage. In developed countries, stroke is among the top 10 causes of death in children. It constitutes 50% of non-traumatic hemorrhages. Trauma is the most common cause of intracerebral hemorrhages, but it should be kept in mind in hemorrhages due to vitamin K deficiency and hemostatic disorders. In infants 2-24 weeks of age, findings may sometimes be subtle. It should be kept in mind that intracranial hemorrhage may develop due to vitamin K deficiency in mothers who use antibiotics for a long time and also in children who are exclusively breastfed. Intracranial hemorrhage has a high morbidity and mortality rate [6-8].

We examined 9 patients who were followed up in our clinic for intracranial hemorrhage due to late vitamin K deficiency in 2020. In this study, we aimed to increase awareness of intracranial hemorrhages due to late vitamin K deficiency, which causes significant morbidity and mortality in the neonatal period.

Material and Methods

Between January 2020 and December 2020, 9 patients who applied to the emergency department with intracranial hemorrhage due to late vitamin K deficiency and were later referred to us were evaluated retrospectively. Vitamin K prophylaxis was not applied to all patients, and other causes of bleeding disorders were excluded. Computer tomography (CT) was taken and types of bleeding on CT, operation status, presence of complications and survival were evaluated. All patients were followed up during their hospitalization.

Statistical analysis

Descriptive statistics were used to describe continuous variables (mean, standard deviation, minimum, median, maximum). Frequency and percentage values were calculated for the descriptive statistics of categorical variables. Comparison of dependent and non-normally distributed continuous variables was made using the Wilcoxon Signed Rank test. Statistical significance level was determined as 0.05. Analyzes were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Four of the patients were female and 5 were male. The mean age of the patients was 8.2+2.7 weeks. Upon admission to the emergency clinic, convulsions were observed in 7 patients (77.8%), fontanel swelling in 6 patients (66.7%), vomiting in 5 patients (55.6%), restlessness in 4 patients (44.4%), irritability in 3 patients (33.3%) and poor sucking (33.3%). Among the symptoms, convulsions were observed most frequently with 25%, followed by swelling in the fontanel in 21.4%, vomiting in 17.9%, restlessness in 14.3%, irritability in 10.7% and poor sucking in 10.7% (Table 1).

It was determined that all patients included in the study did not receive prophylactic postnatal vitamin K. International normalized ratio (INR) values of the patients at admission were checked, and the mean was found to be 4.2 + 1.1. Control INR values of the patients were checked after vitamin K was administered. The mean of the control INR value was found to be 1.1+0.1 (Table 2). The change in INR value was found to be statistically significant.

Table 1. Demographic Data and Arrival Complaint

	N	%	
Gender			
Female	4	44,4	
Male	5	55,6	
	Average + SD	**Med (min-max)**	
Age (weeks)	8,2+2,7	8 (3-12)	
	N	**%[1]**	**%[2]**
Poor sucking	3	10,7	33,3
Swelling in the fontanel	6	21,4	66,7
Restlessness	4	14,3	44,4
Irritability	3	10,7	33,3
Convulsion	7	25	77,8
Vomiting	5	17,9	55,6
Total	28	100	33,3

[1] Percentage of all complaints, [2] Percentage of the total number of patients

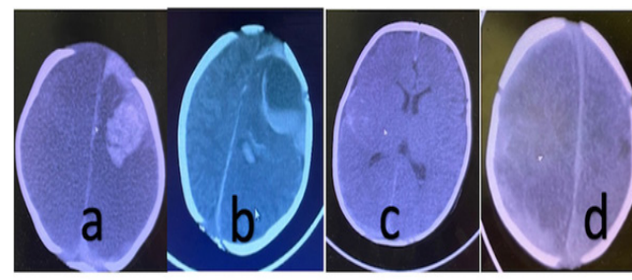

Figure 1. Patient CT Scans
a: Intraparenchymal hemorrhage + subdural hemorrhage
b: Intraparenchymal hemorrhage + subdural hemorrhage + subarachnoid hemorrhage c: subarachnoid hemorrhage
d: subdural hemorrhage + subarachnoid hemorrhage

Table 2. Patients' INR Values

	Arrival INR	INR After Vitamin K	p
Mean+SD	4,2+1,1	1,1+0,1	0,008
Med (min-max)	4,3(2,6-6,3)	1,1(0,8-1,3)	

*Wilcoxon Signed Rank test

Table 3. Type of Bleeding, Operation, Postoperative Complications and Latest Situation.

	N	%
SAH	1	11,1
SAH+SDH	4	44,4
SAH+SDH+IPH	3	33,3
SDH+IPH	1	11,1
Total	9	100
	N	**%**
Operation		
Yes	3	33,3
No	6	66,7
Complication	9	100
hemiplegia	2	66,7
hydrocephalus	1	33,3
Outcome		
Deceased	2	22,2
Alive	7	77,8

IPH: Intraparenchymal hemorrhage, SAH: Subarachnoid Hemorrhage, SDH: Subdural Hemorrhage

Radiological imaging detected subarachnoid hemorrhage (SAH) + subdural hemorrhage (SDH) in 4 patients, SAH + SDH +intraparenchymal hemorrhage (IPH) in 3 patients, SAH + IPH in 1 patient, and SAH in 1 patient (Table 3) (Figure a, b, c, d).

In the follow-up of the cases, surgical intervention was performed in 3 patients (33.3%). Hydrocephalus developed in one patient who underwent surgery during the follow-up period and a ventriculoperitoneal shunt system was applied. Two patients who were not operated on died due to general complications during the intensive care follow-up period. The remaining 7 patients survived. Hemiplegia developed in 2 patients who did not undergo surgery. The patients were included in the physical therapy program for rehabilitation. In the follow-up, the patients' strengths recovered almost completely (Table 3).

There was a statistically significant difference between INR on arrival and INR after Vitamin K.

Discussion

Late VKDB develops as a result of insufficient plasma concentration of active coagulation factors II, VII, IX and X. Although it usually occurs between the 2nd and 12th weeks, when studying the literature, it is reported that the cases can be seen up to 6 months of age. Although vitamin K crosses the placenta, its serum level is not sufficient. The plasma concentration of vitamin K varies between 30% and 60% compared to the normal adults. The concentration of vitamin K in breast milk is physiologically low (breast milk level 1-4mg/L) [5]. According to the study by Pirinccioglu et al, 93.7% of babies are exclusively breastfed for the first 6 months [9]. Considering this high rate, it can be predicted that the risk of late VKDB due to vitamin K deficiency may rise to high rates [10]. It has been stated that there is a risk of bleeding between 50-80% in late VKDB, and it has been observed that the incidence of intracranial hemorrhages has increased. When we examined the literature in terms of bleeding types, we saw that the distribution of bleeding types was different. In the study by Visser et al. on 16 patients, SDH was detected most frequently in 50% [11]. In the study by Zidan et al on 32 patients, SDH was observed in 56.3% of the patients, IPH was observed in 31.3%, and mixed-type bleeding was observed in 12.5% of the patients [12]. Ozdemir et al. in their study on 120 patients found SDH in 28%, IPH in 23%, SAH in 14%, intraventricular bleeding in 8%, IPH+SDH bleeding in 10%, and SDH+SAH in 5% [2]. In our study, we found the most common mixed-type bleeding at 88.9%. We observed only SAH in 1 patient (11.1%). The most common type of bleeding was SDH and SAH with 8 patients in our study. It was followed by IPH in 4 patients. When we compared our study with the literature, we found that mixed-type bleeding was more common and parallel to the literature in terms of bleeding type. Late VKDB clinical findings are non-specific. It may present with clinical findings such as seizure, fever, vomiting, unconsciousness, generalized hypotonia, impaired sucking, irritability, pallor, and fontanel swelling [9, 12]. Princcioglu et al. in their study conducted with 31 patients found pallor in 24 patients (77.4%), seizures in 18 patients (58%), confusion in 18 patients (18%), vomiting in 14 patients (44%), malnutrition in 11 patients (35%), fontanel pulsation in 19 patients (61%) and swelling in 8 patients (26%) [9]. Our study shows parallelism with the literature in terms of symptoms. Although the most common complaint is seizure, it is respectively followed by swelling in the fontanel, vomiting, restlessness, poor sucking and irritability.

Although late VKDB causes severe neurological sequelae and death, its incidence varies according to the development level of the countries. In a study conducted in Germany, 21% morbidity and 19% mortality were found. In another study conducted in Egypt, mortality was found to be higher with 23.8%. In another study conducted in our country, mortality was 20.8% and morbidity was 48.1% [13]. In our study, 2 patients (22.2%) died due to general complications during the intensive care follow-up period. Hemiplegia developed in 2 non-operated patients and hydrocephalus in 1 operated patient. The literature reports that the incidence of hydrocephalus after intracerebral hemorrhage ranges from 8.9% to 50% depending on the type of bleeding [13]. Hydrocephalus finding is accepted as a poor prognosis finding [14, 15]. Our rate was 33.3%. Ventriculoperitoneal shunt system was applied to the patient who developed hydrocephalus. When our results were compared with the literature, parallelism was observed again.

Prothrombin time (PT) and active partial thromboplastin time (aPTT) values are prolonged in vitamin K deficiency. It is known that bleeding values return to normal within 2-3 hours with the administration of vitamin K [3]. Considering the reasons for not taking vitamin K prophylaxis in our study, it was observed that some cases were not chosen by their parents, and some

cases were born at home and subsequently could not access health services. We found that the INR values of the cases were observed to be high at the time of admission and after vitamin K was administered to all cases, the INR values returned to normal. According to our findings, all newborn infants should be given vitamin K prophylaxis to avoid the catastrophic effects of VKDB. Vitamin K prophylaxis can be administered orally or intramuscularly. It has been observed that the oral form is less effective in reducing the risk of ICH than the intramuscular form. Although there are articles that vitamin K prophylaxis may increase the incidence of some childhood cancers, the discussions about this have not been clarified [2, 3, 16].

Conclusion

Although late VKDB is seen between the 2nd and 12th weeks on average, it can be seen up to the 6th month. The morbidity and mortality of late VKDB are high, and it mostly presents with intracranial hemorrhages. Breast milk is poor in terms of vitamin K content, and considering that the majority of newborn babies are fed only with breast milk for the first 6 months, it is seen how high the risk is. The way to reduce this risk is that it is important to administer vitamin K prophylaxis, especially in its intramuscular form. Prophylaxis should be made mandatory and should be applied to all newborns born in or out of the hospital. In this way, morbidity and mortality that may occur in VKDB can be prevented. We can prevent information pollution by providing pregnant women with accurate information about vitamin K prophylaxis during pregnancy follow-up.

Our study was conducted with a limited number of patients. Prophylaxis has become widespread with the increase in routine follow-ups in children. Its incidence has decreased in parallel with the developments in diagnosis and treatment. However, it should be kept in mind that when prophylaxis is not performed, it can cause all kinds of intracranial hemorrhage and lead to serious sequelae and death, as seen in our study.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Arendt DH, Hegdahl DA, Hsu BA, Wagner KJ. Intracranial Hemorrhage Secondary to Vitamin K Deficiency Bleeding in a Newborn. S D Med. 2022; 75(5): 220-3.

2. Ozdemir MA, Karakukcu M, Per H, Unal E, Gumus H, Patiroglu T. Late-type vitamin K deficiency bleeding: experience from 120 patients. Childs Nerv Syst. 2012; 28(2): 247-51.

3. Schulte R, Jordan LC, Murad A, Naftel RP, Wellons JC, Sidonio R. Rise in Late Onset Vitamin K Deficiency Bleeding in Young Infants Because of Omission or Refusal of Prophylaxis at Birth. Pediatr Neurol. 2014; 50(6): 564-8.

4. Sellers A, Lew A, Tudyk M, Nakagawa TA, Sochet AA. Hemorrhagic Disease of the Newborn: A Case Series Illustrating Preventable Harm. J Pediatr Health Care. 2023; 37(1): 67-73.

5. Klironomi I, Celaj E, Kola E, Lluka R, Sala D, Kito I, et al. Intracranial hemorrhage due to late vitamin K deficiency in infants in Albania. Paediatr Croat. 2014; 58(2): 101-6.

6. Elalfy M, Eltonbary K, Elalfy O, Gadallah M, Zidan A, Abdel-Hady H. Intracranial haemorrhage associated with Vitamin K deficiency in Egyptian infants. Acta Paediatr. 2021; 110(11): 2937-43.

7. Rajeev A, Chawla N. Unusual presentation of late vitamin K deficiency bleeding in an infant. Med J Armed Forces India. 2016; 72(Suppl. 1): S142-3.

8. Yilmaz C, Yuca SA, Yilmaz N, Bektas MS, Caksen H. Intracranial hemorrhage due to vitamin K deficiency in infants: a clinical study. Int J Neurosci. 2009; 119(12): 2250-6.

9. Pirinccioglu AG, Gurkan F, Bosnak M, Acemoglu H, Davutoglu M. Intracranial hemorrhage: clinical and demographic features of patients with late hemorrhagic disease. Pediatr Int. 2011; 53(1): 68-71.

10. Karaci M, Toroslu E, Karsli T, Kanber Y, Uysal S, Albayrak D. Intracranial Haemorrhage Due to Late-Onset Vitamin K Deficiency. HK J Paediatr (New Series). 2015; 20:80-5

11. Visser DY, Jansen NJ, Ijland MM, Konig TJ, Hasselt PM. Intracranial bleeding due to vitamin K deficiency: advantages of using a pediatric intensive care registry. Intensive Care Med. 2011; 37(6): 1014–20.

12. Zidan AS, Abdel-Hady H. Surgical evacuation of neonatal intracranial hemorrhage due to vitamin K deficiency bleeding. J Neurosurg Pediatr. 2011; 7(3): 295-9.

13. Hu R, Zhang C, Xia J, Ge H, Zhong J, Fang X, et al. Long-term Outcomes and Risk Factors Related to Hydrocephalus After Intracerebral Hemorrhage. Transl Stroke Res. 2021; 12(1): 31-8.

14. Bhattathiri PS, Gregson B, Prasad KS, Mendelow AD, Investigators S. Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. Acta Neurochir Suppl. 2006; 96:65-8.

15. Xi G, Strahle J, Hua Y, Keep RF. Progress in translational research on intracerebral hemorrhage: is there an end in sight? Prog Neurobiol. 2014; 115:45-63.

16. Unal E, Ozsoylu S, Bayram A, Ozdemir MA, Yılmaz E, Canpolat M, et al. Intracranial hemorrhage in infants as a serious, and preventable consequence of late form of vitamin K deficiency: A selfie picture of Turkey, strategies for tomorrow. Childs Nerv Syst. 2014; 30(8):1375-82.

How to cite this article:

Barış Erdoğan, Duygu Ceman. *Retrospective evaluation of patients with intracranial bleeding due to late vitamin K deficiency. Ann Clin Anal Med 2023;14(Suppl 1):S22-25*

This study was approved by the Ethics Committee of Harran University (Date: 2021-12-27, No: HRU/21.23.01).